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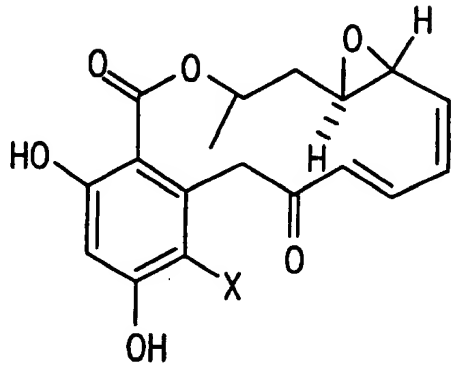
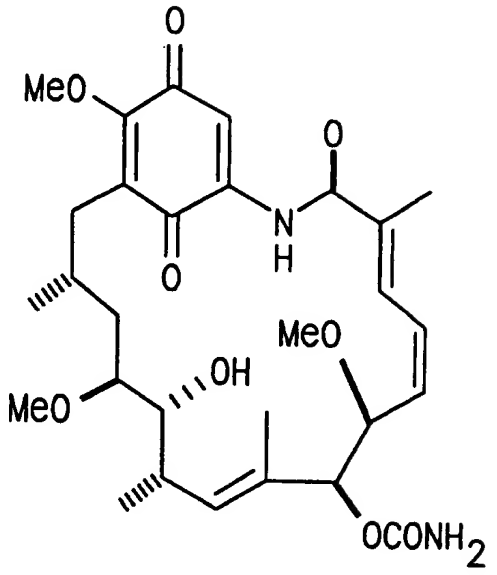
FIG. 1



X=Cl Radicicol (1)

X=H Monocillin I (2)



Geldanamycin (3)

FIG.2

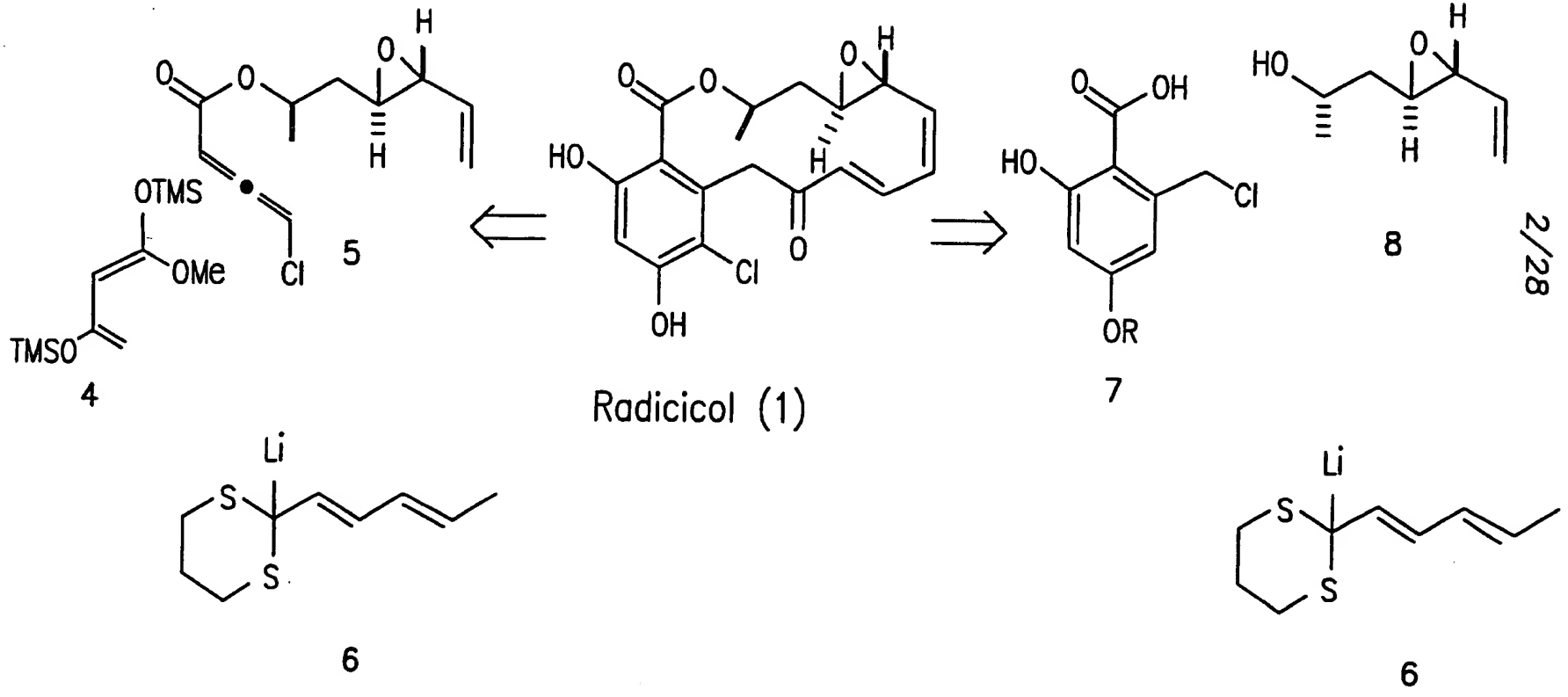
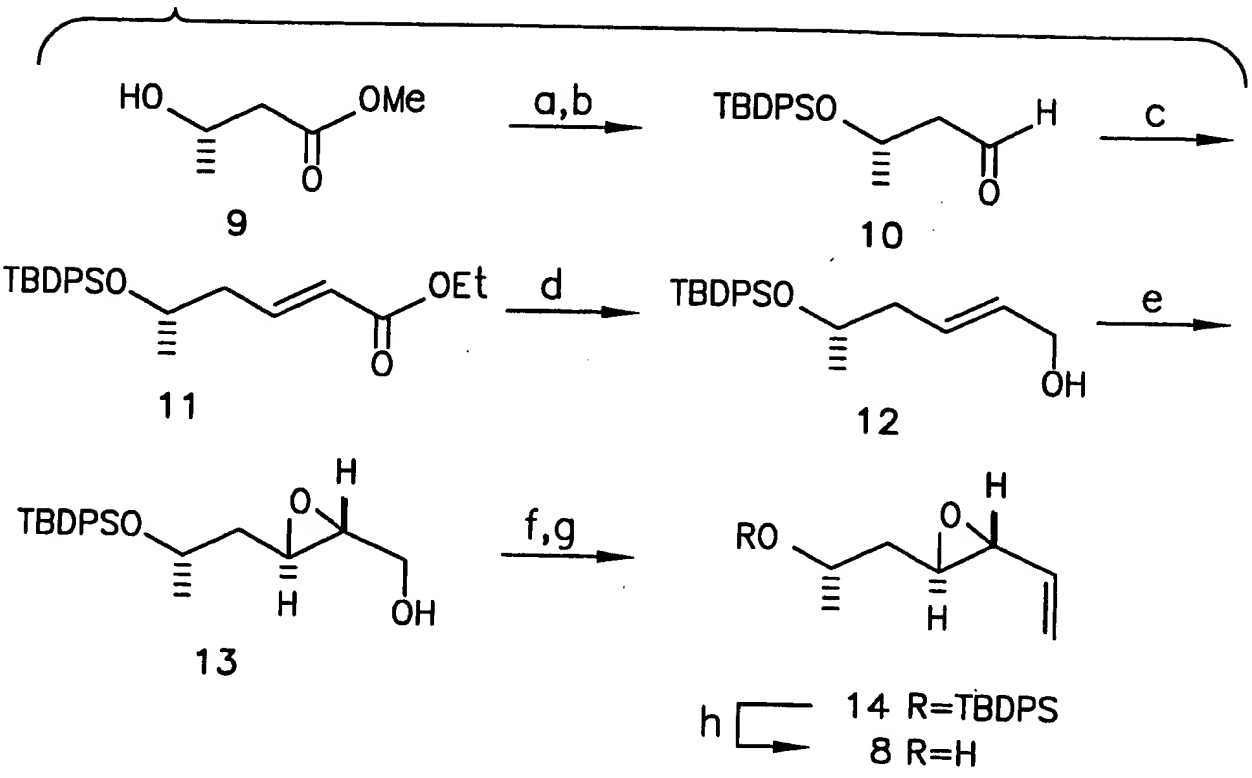
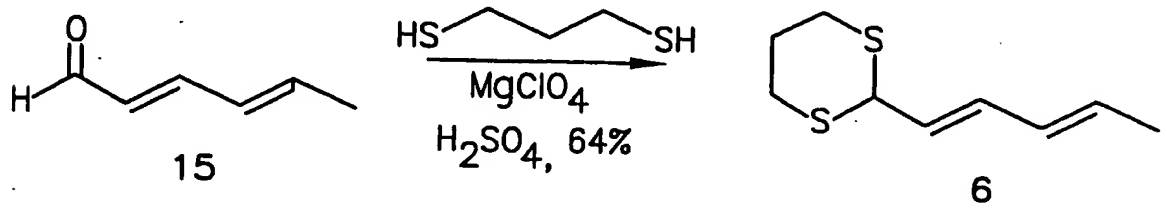


FIG. 3



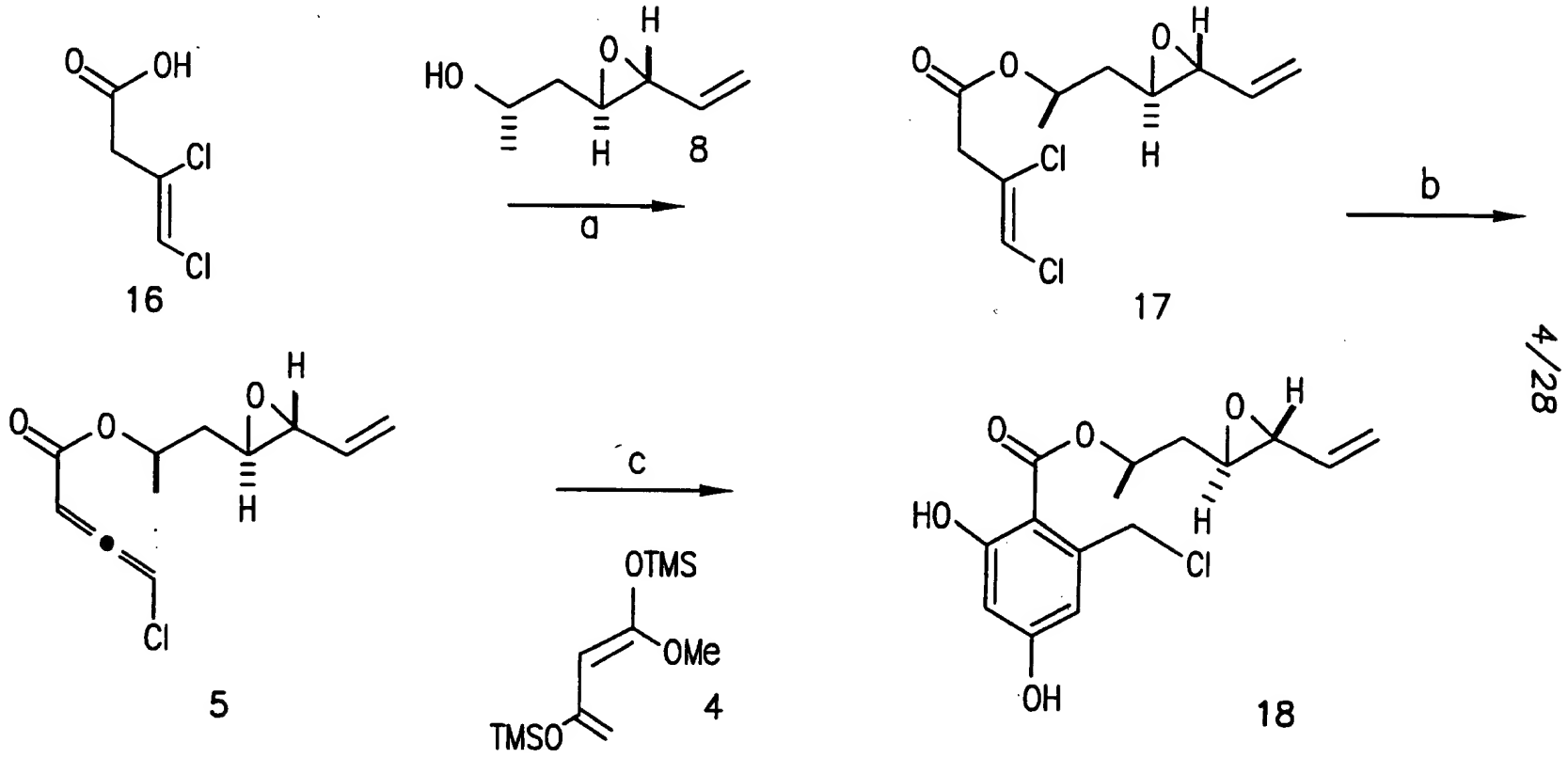
(a) TBDPSCl, imid.,>95%; (b) DIBAL–H,–78 °C, 92%;
(c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%;
(d) DIBAL–H, –20 °C, 96%; (e) (+)–DET, $Ti(OiPr_4)$, TBHP,90%,>95%ee; (f) SO_3*pyridine, Et_3N, DMSO, 90%;
(g) PH_3PCH_3Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.



15

6

FIG. 4



(a) DEAD, PPh_3, 70%; (b.) iPr_2NEt, 70%; (c.) 50% (4:1)

FIG.5

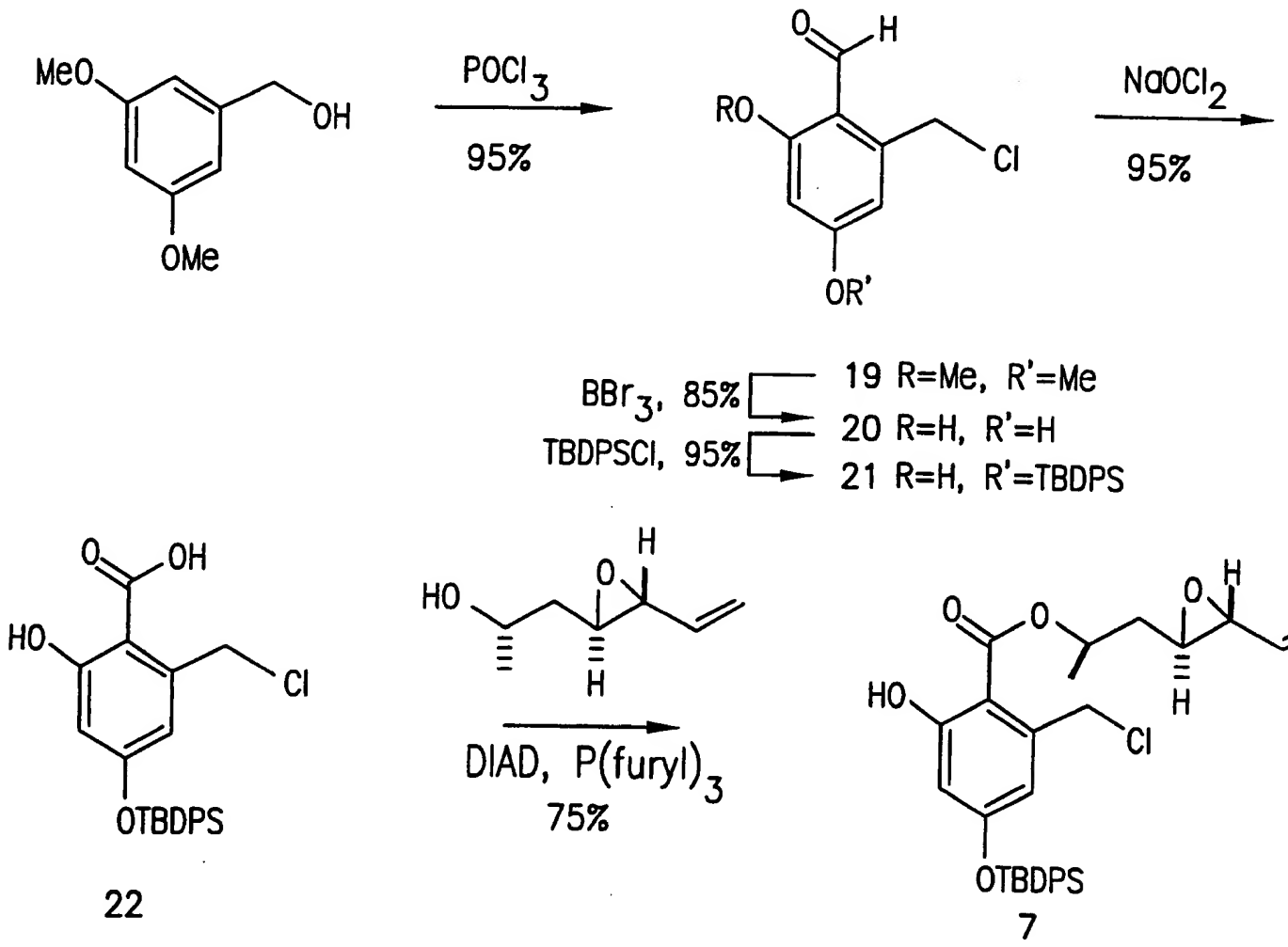
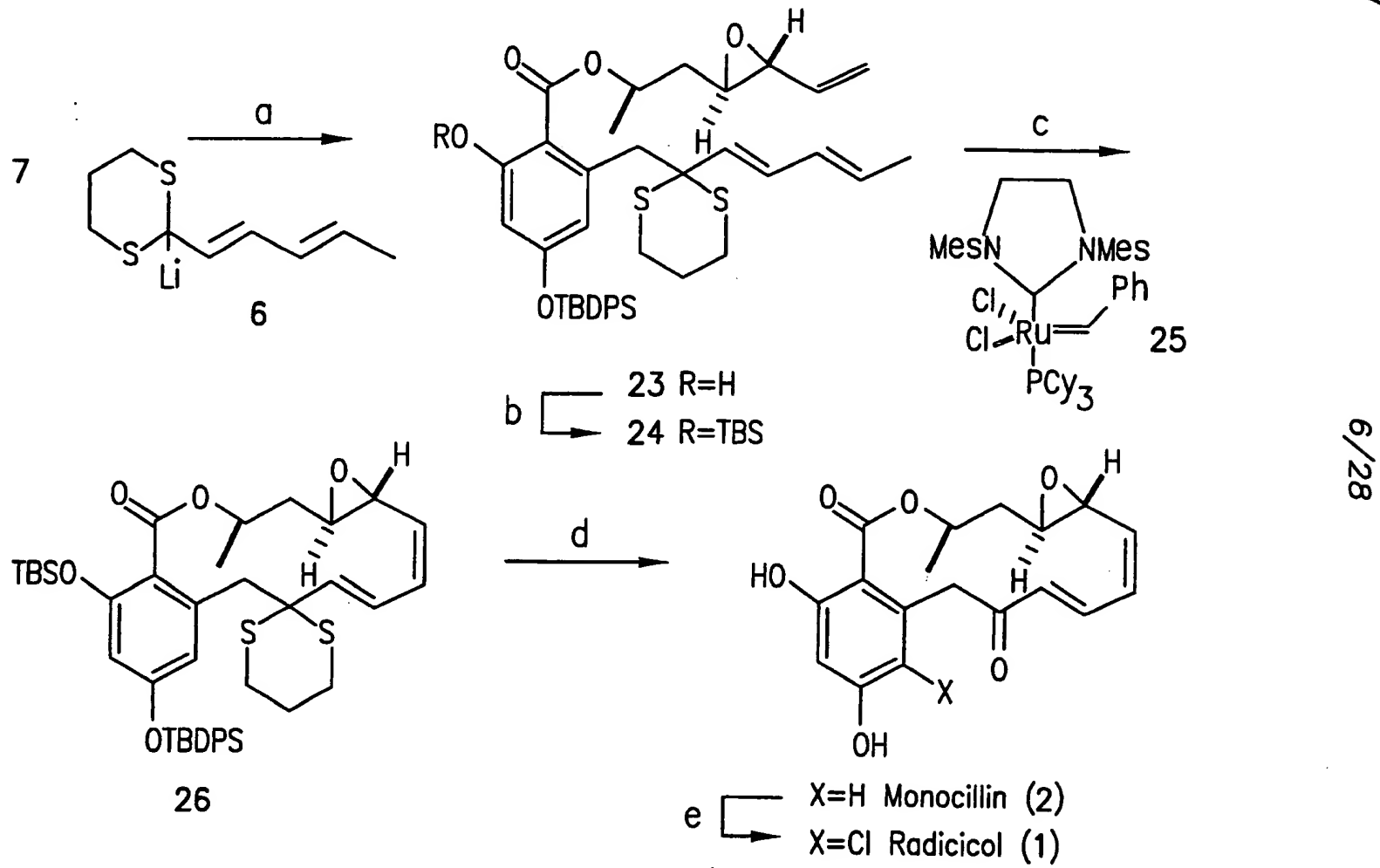

MeO
OH
OMe
POCl3
95%
O
H
RO
Cl
OR'
NaOCl2
95%
BBr3, 85%
TBDPSCl, 95%
19 R=Me, R'=Me
20 R=H, R'=H
21 R=H, R'=TBDPS
O
OH
HO
Cl
OTBDPS
22
H
O
HO
H
DIAD, P(furyl)3
75%
O
O
O
H
HO
Cl
H
OTBDPS
7

FIG. 6



a. n–BuLi, –78 °C, 50% (6:1); b. TBSCl, 83%; c. 42 C, 70%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 °C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 50%

FIG. 7

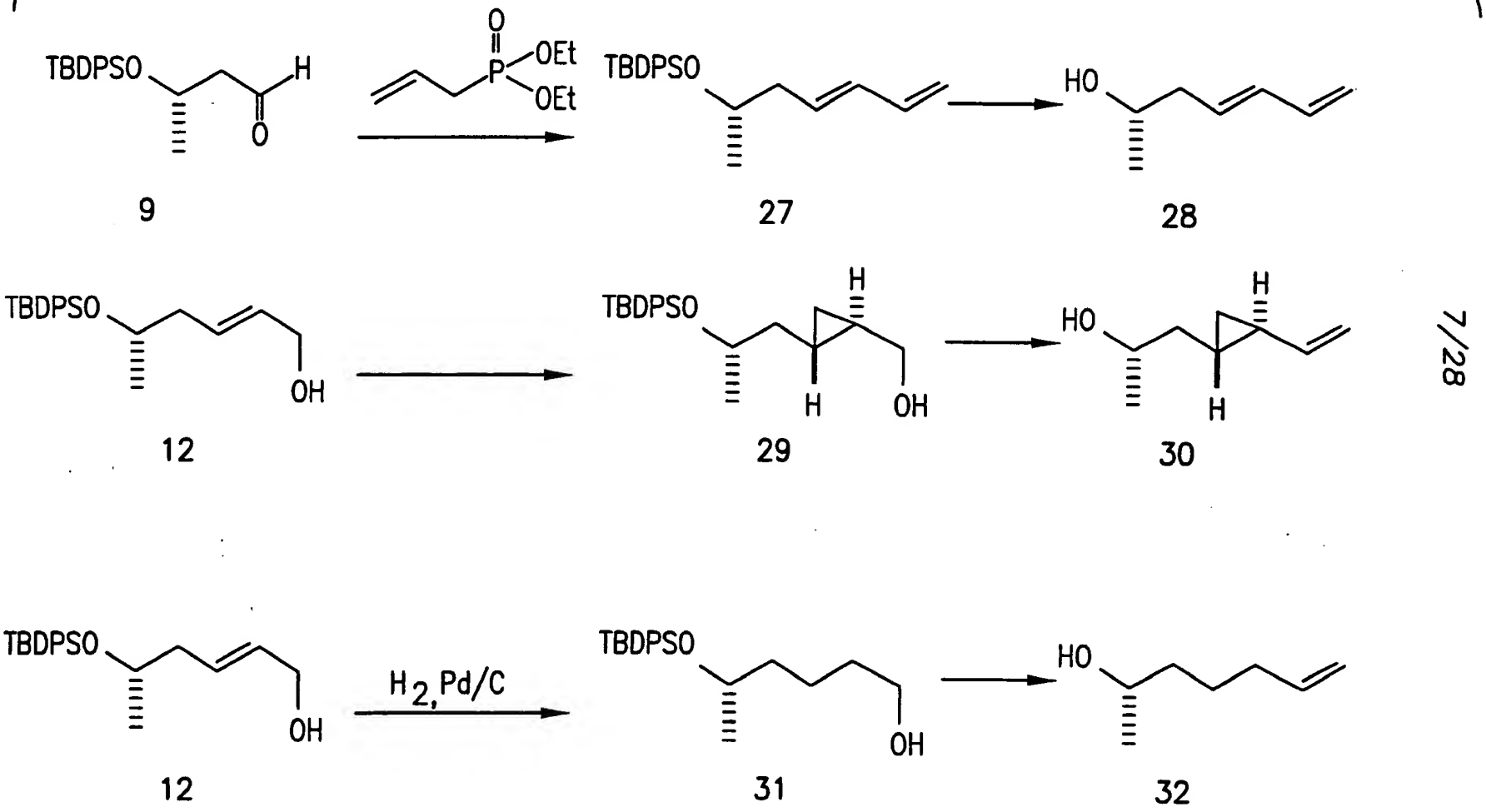
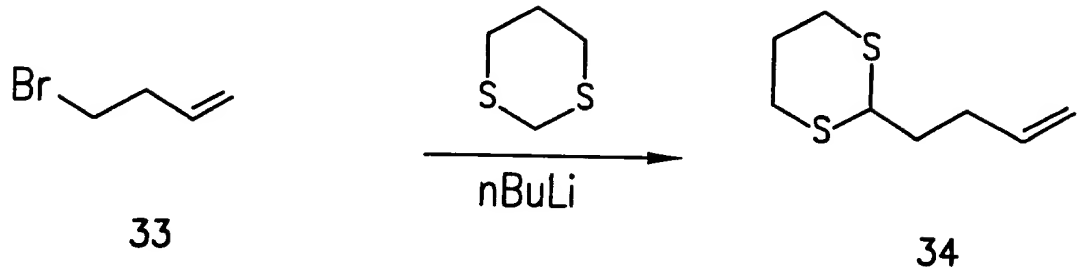

TBDPSO
H
O
O
P
OEt
OEt
9
TBDPSO
27
HO
28
TBDPSO
OH
12
TBDPSO
H
H
OH
29
HO
H
H
30
TBDPSO
OH
12
H2, Pd/C
TBDPSO
OH
31
HO
32

FIG.8



33

34

FIG. 9

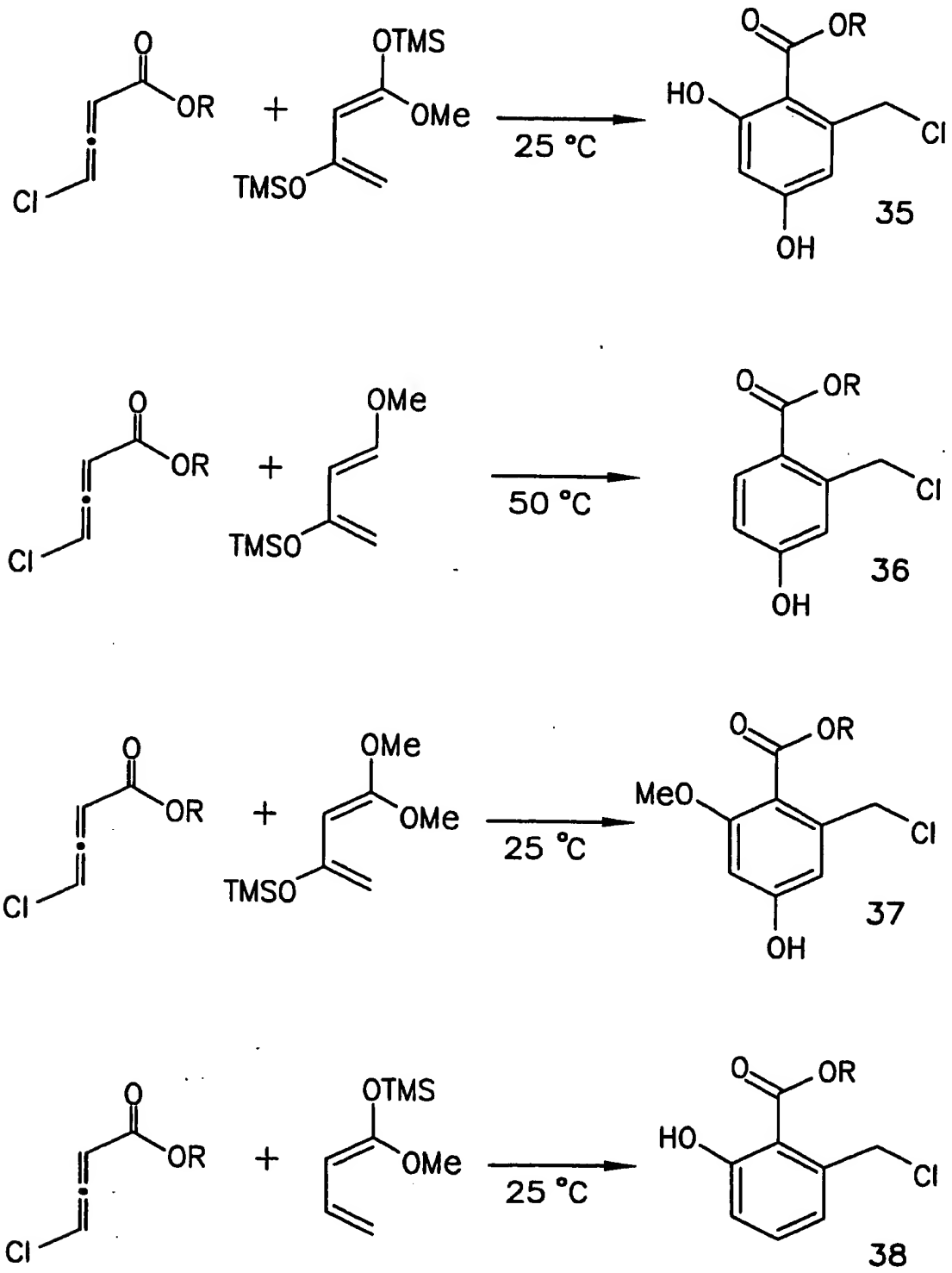
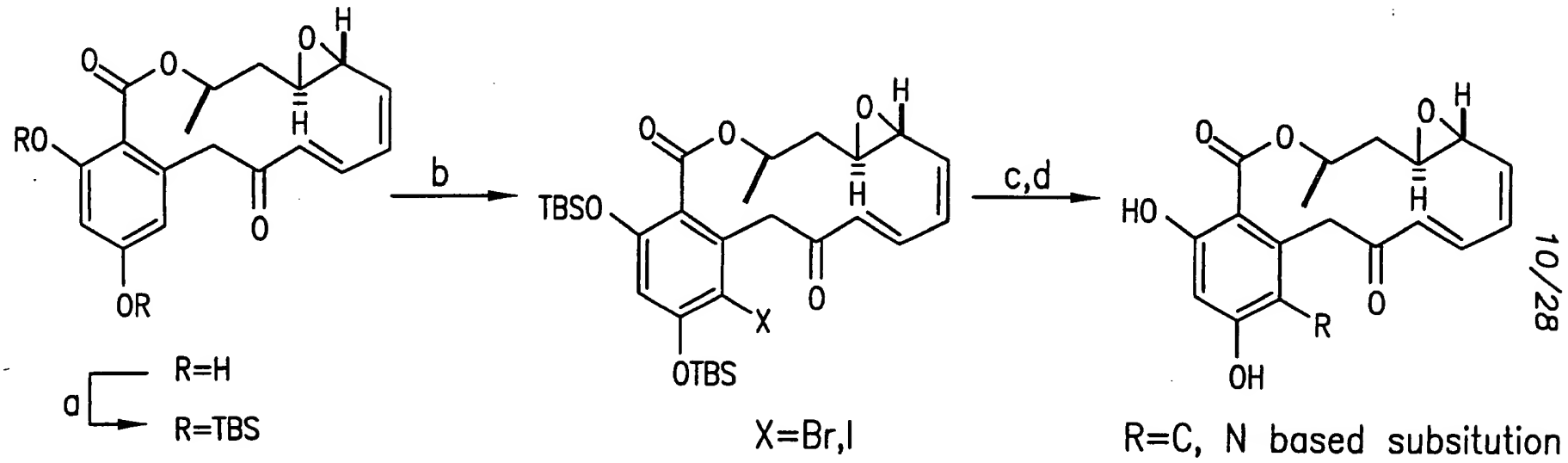
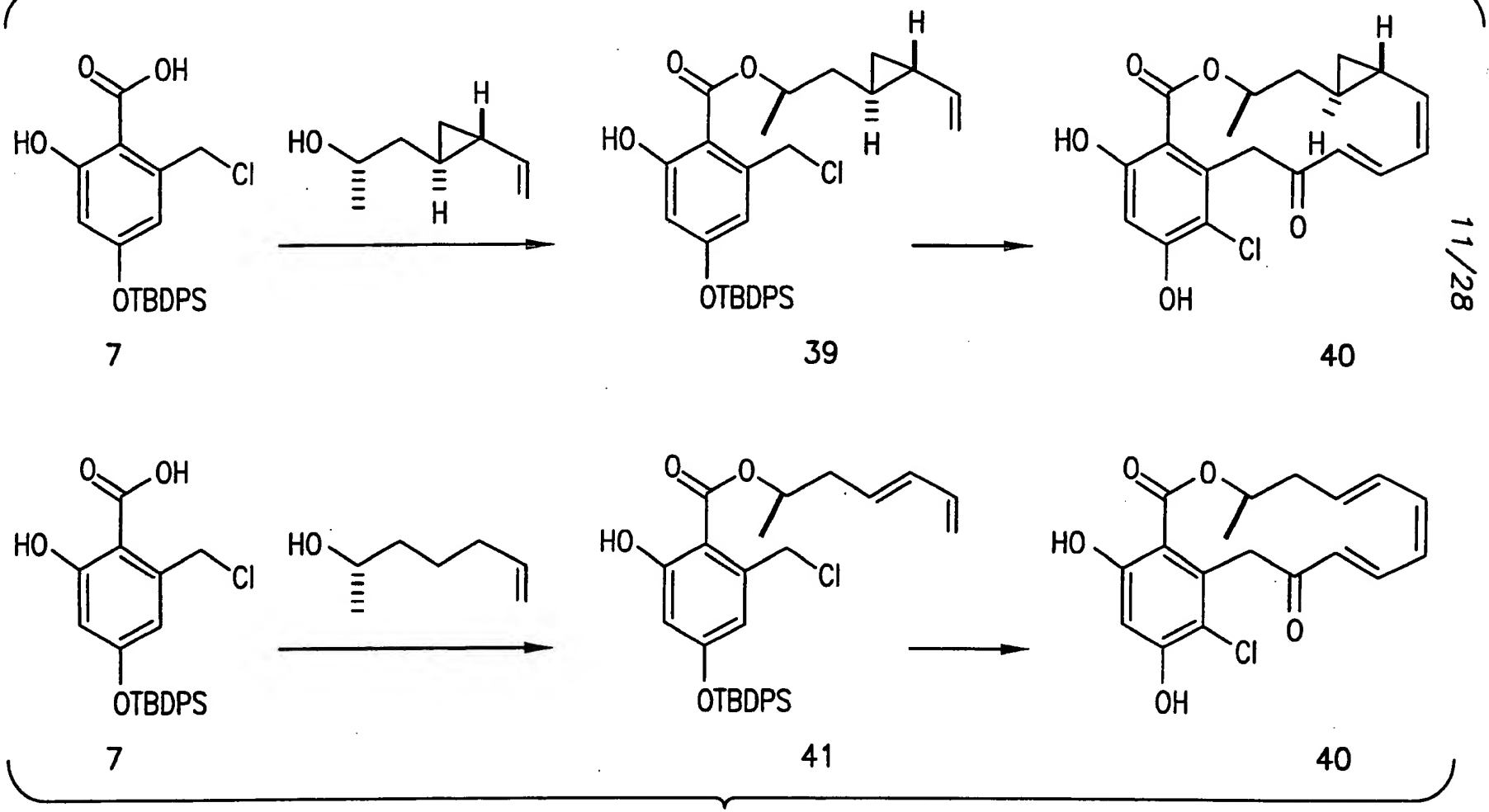


FIG. 10



a. TBSCl, pyridine; b. NIS or NBS, TsOH; c. $Pd(PPh)_3$, $RSnBu_3$, d. nBu_4NF

FIG. 11-1



TO FIG. 11-2

FROM FIG. 11-1

FIG. 11-2

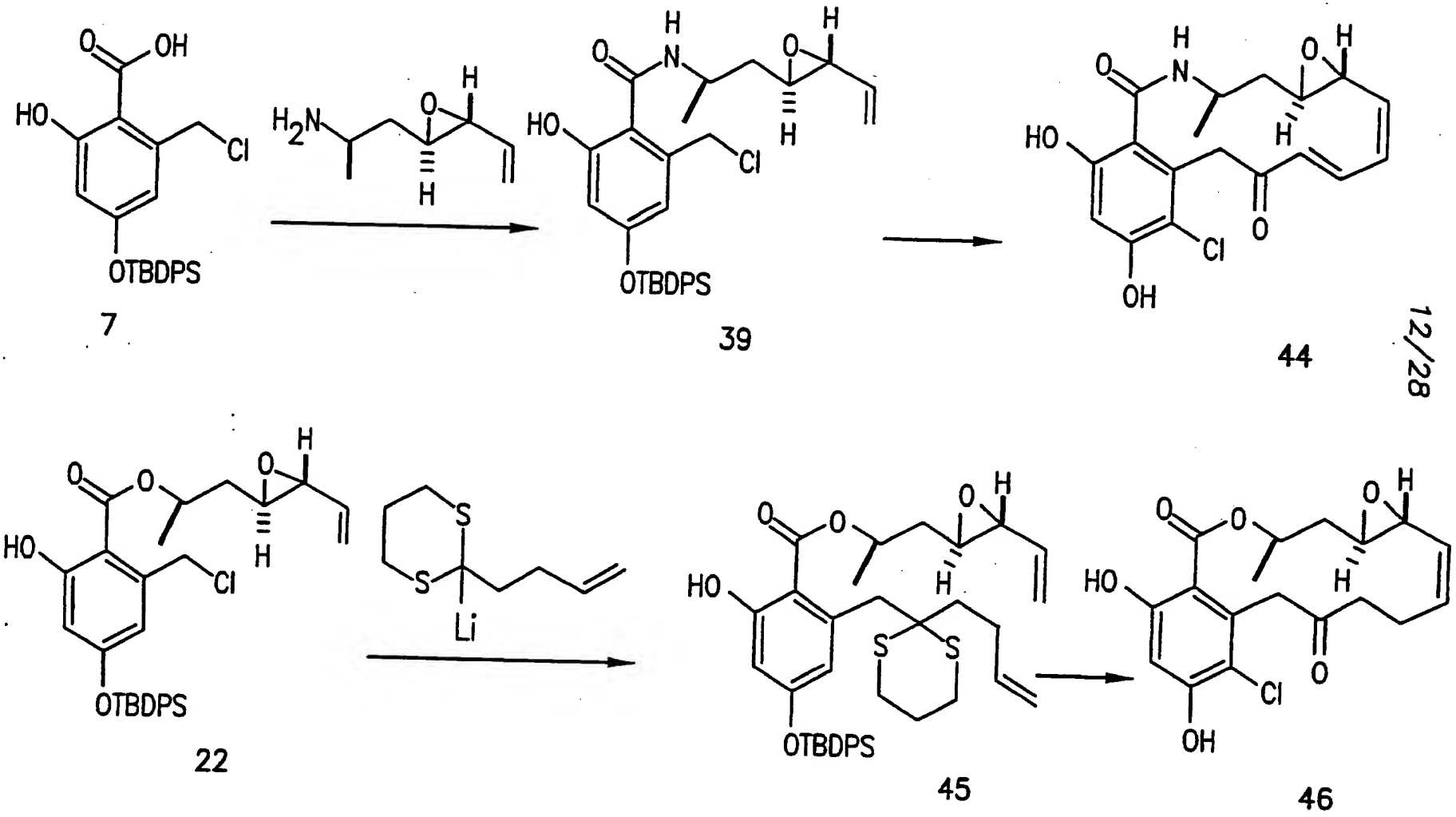
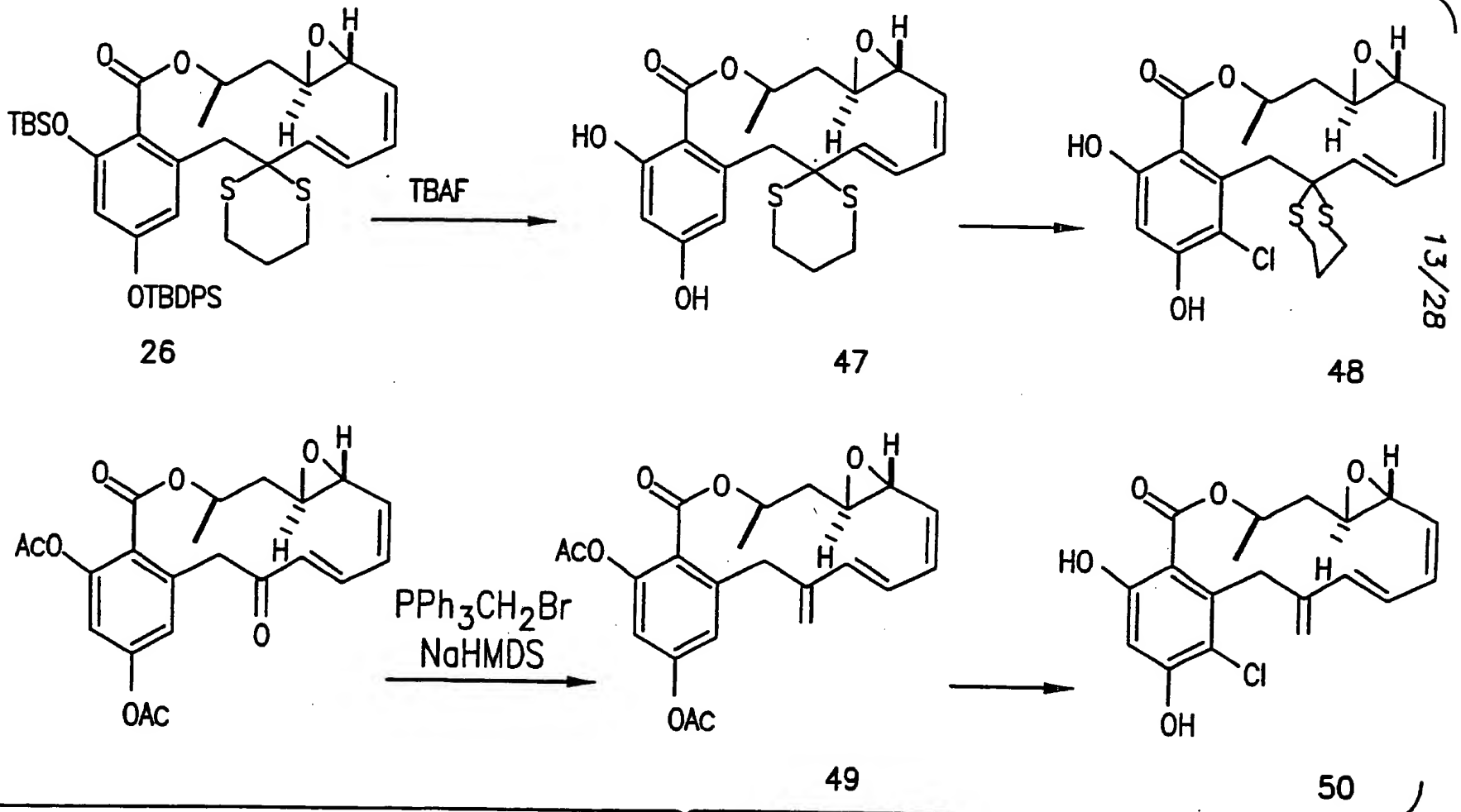


FIG. 12-1



TO FIG. 12-2

FROM FIG. 12-1

FIG. 12-2

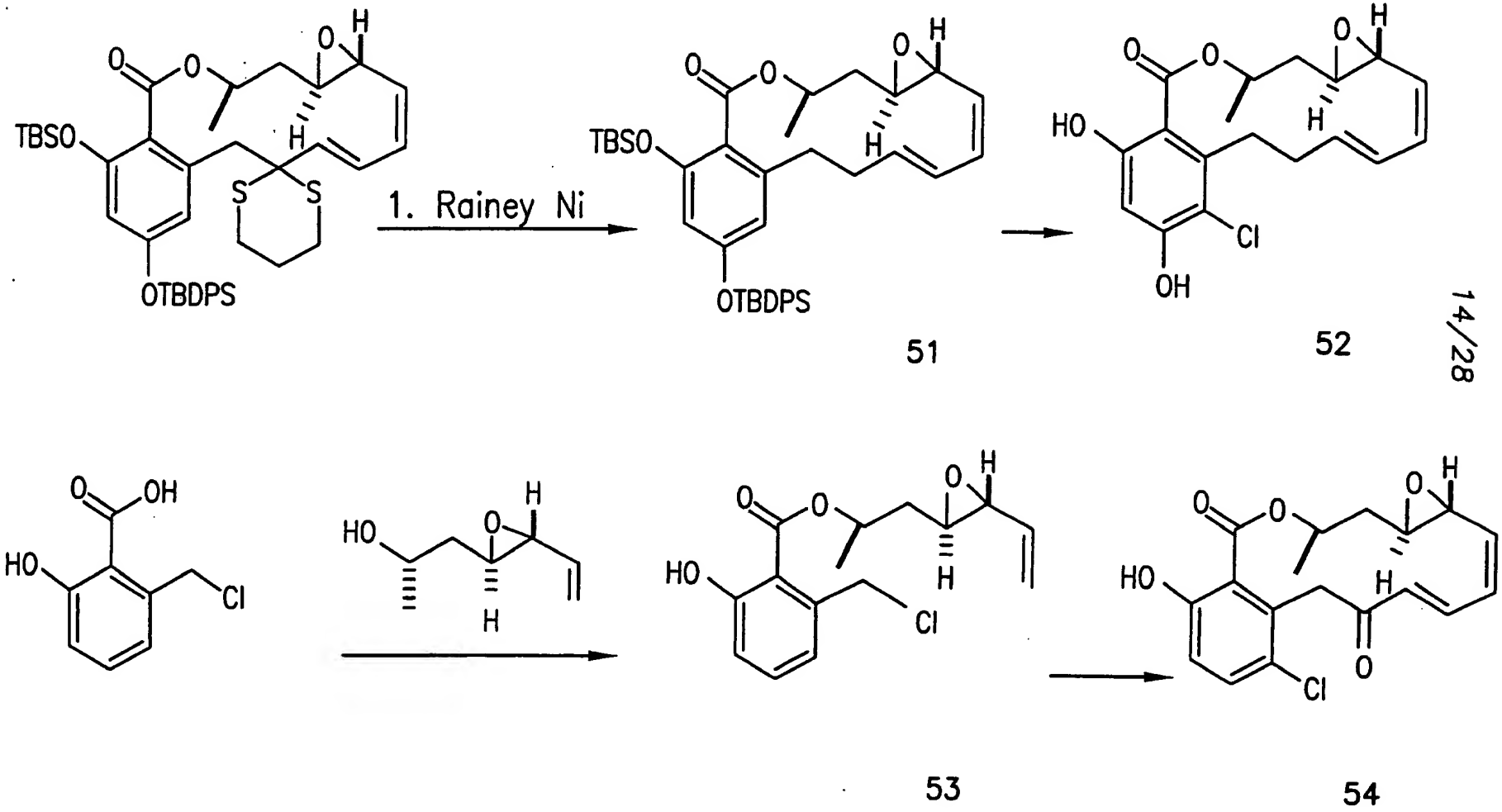
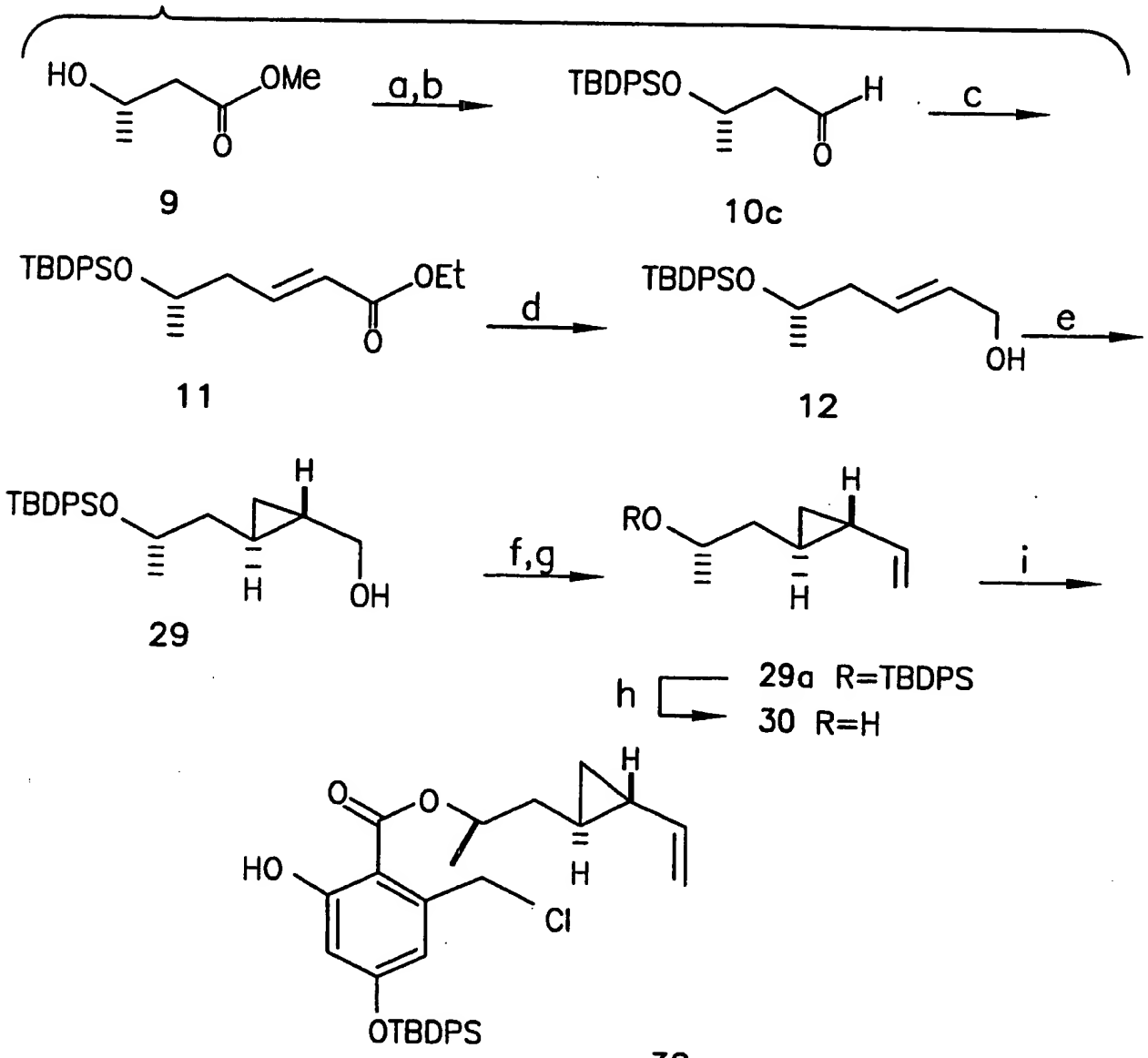
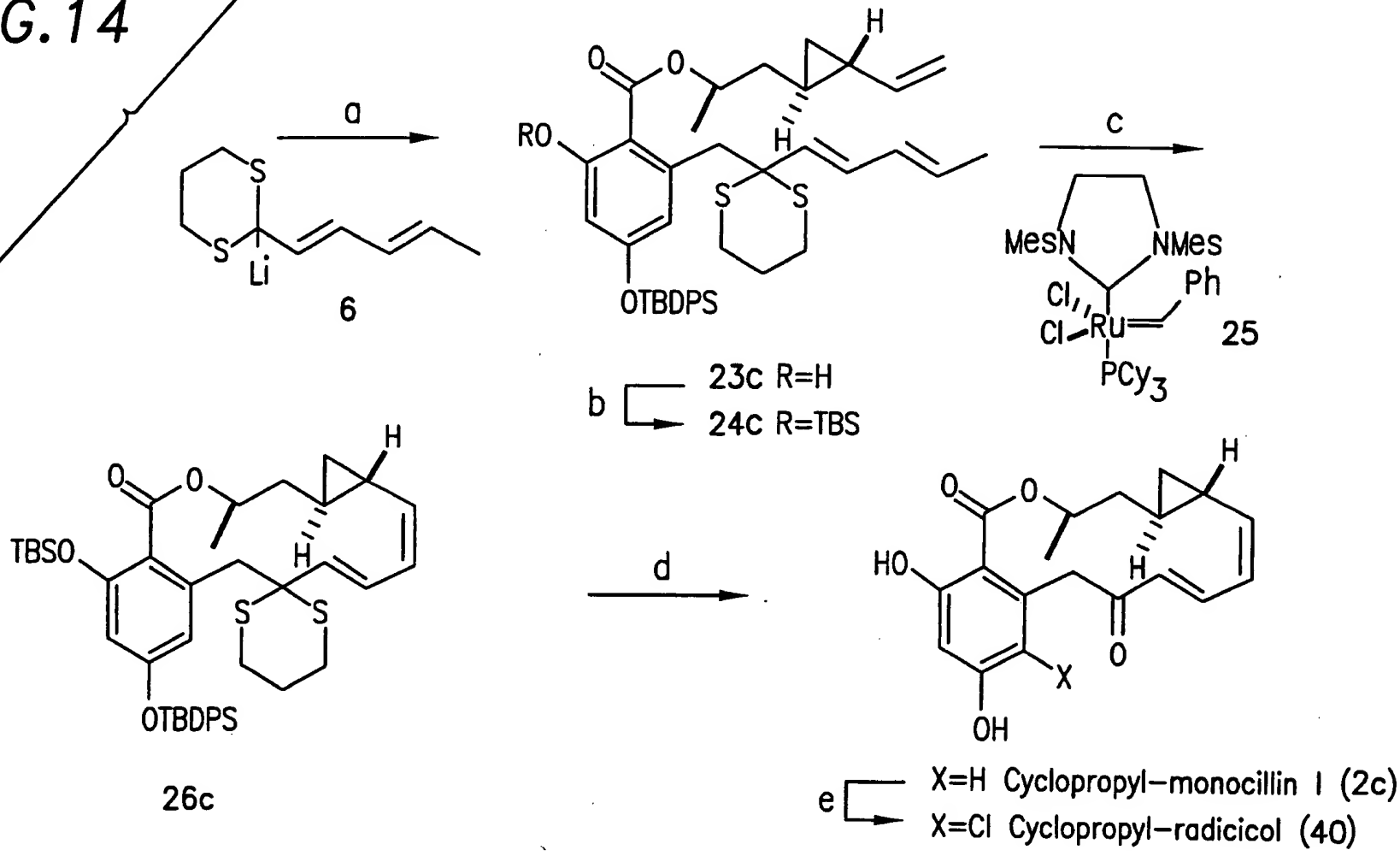


FIG. 13



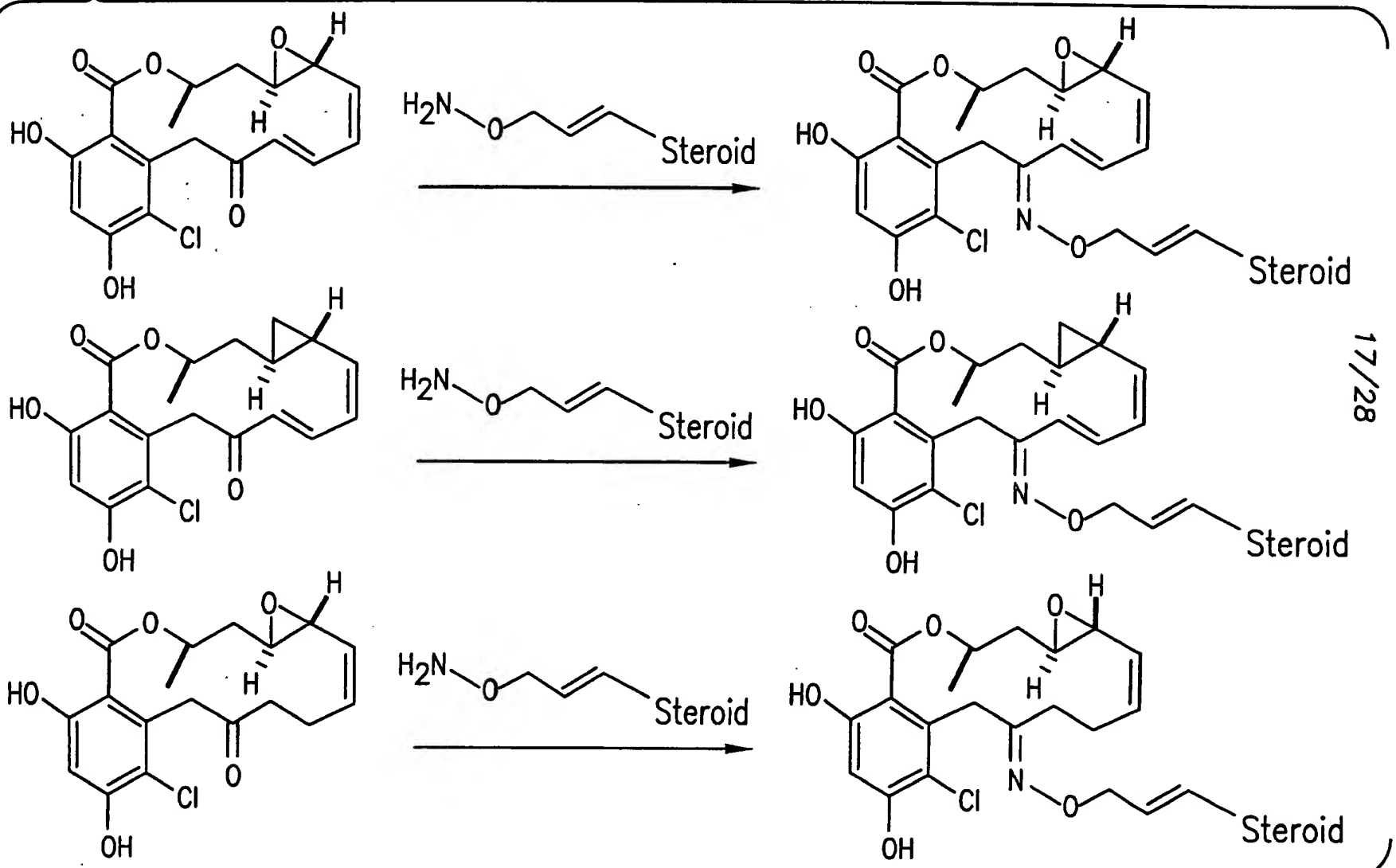
[a] (a) TBDPSCl, imid.,>95%; (b) DIBAL–H,–78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL–H –20 °C, 96%; (e) (+)–tetramethyltartaricacid diamide–BBu, Et_2Zn, CH_2I_2, 9 >95% ee; (f) SO_3*pyridine, Et_3N, DMSO, 90%; (g) Ph_3 PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7, $P(furyl)_3$, DIA benzene, 60%

FIG. 14



a. n–BuLi, −78 °C, 75% (3:1); b. TBSCl, 83%; c. 42 °C, 20%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 °C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 80%

FIG. 15-1



TO FIG. 15-2

FROM FIG. 15-1

FIG. 15-2

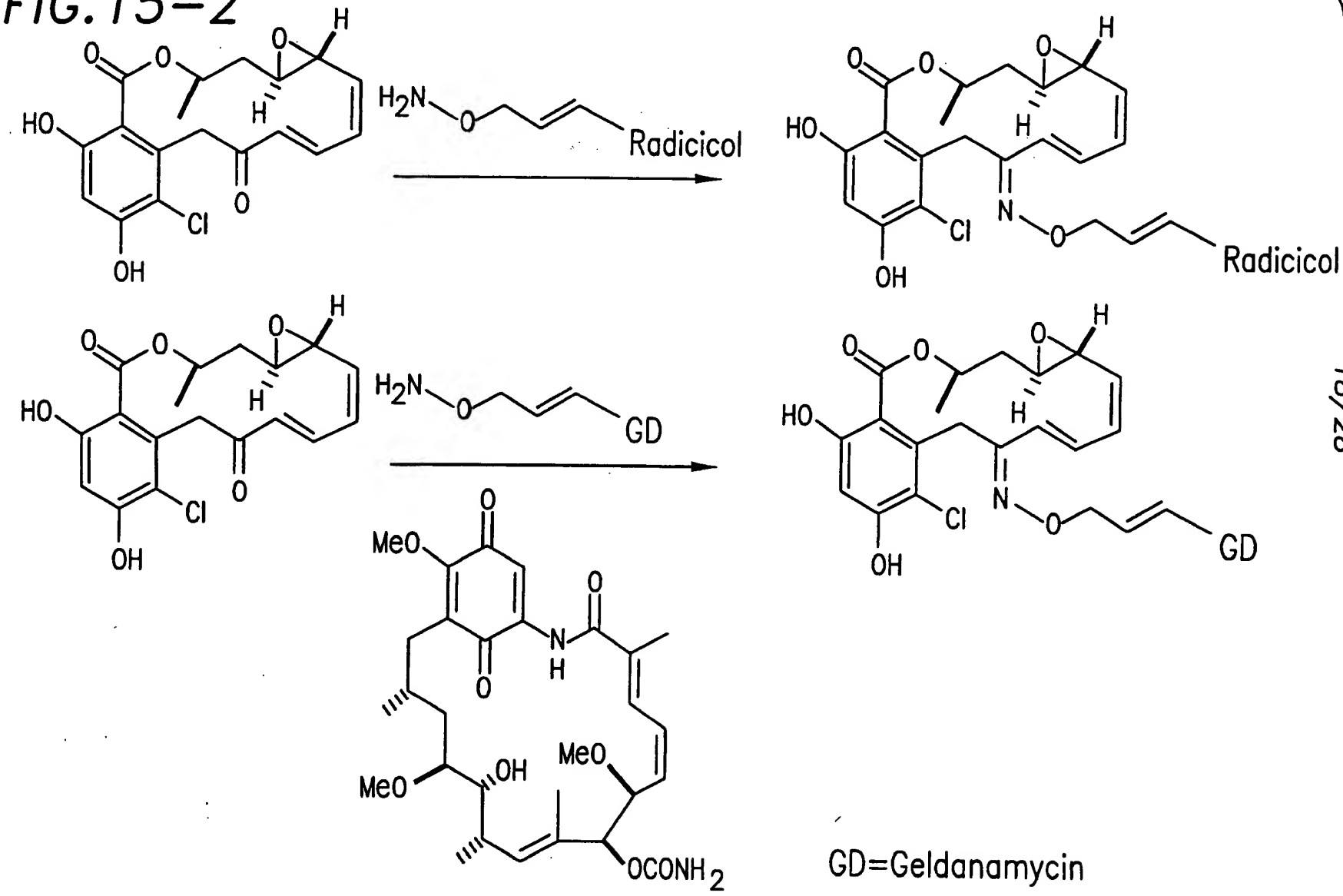
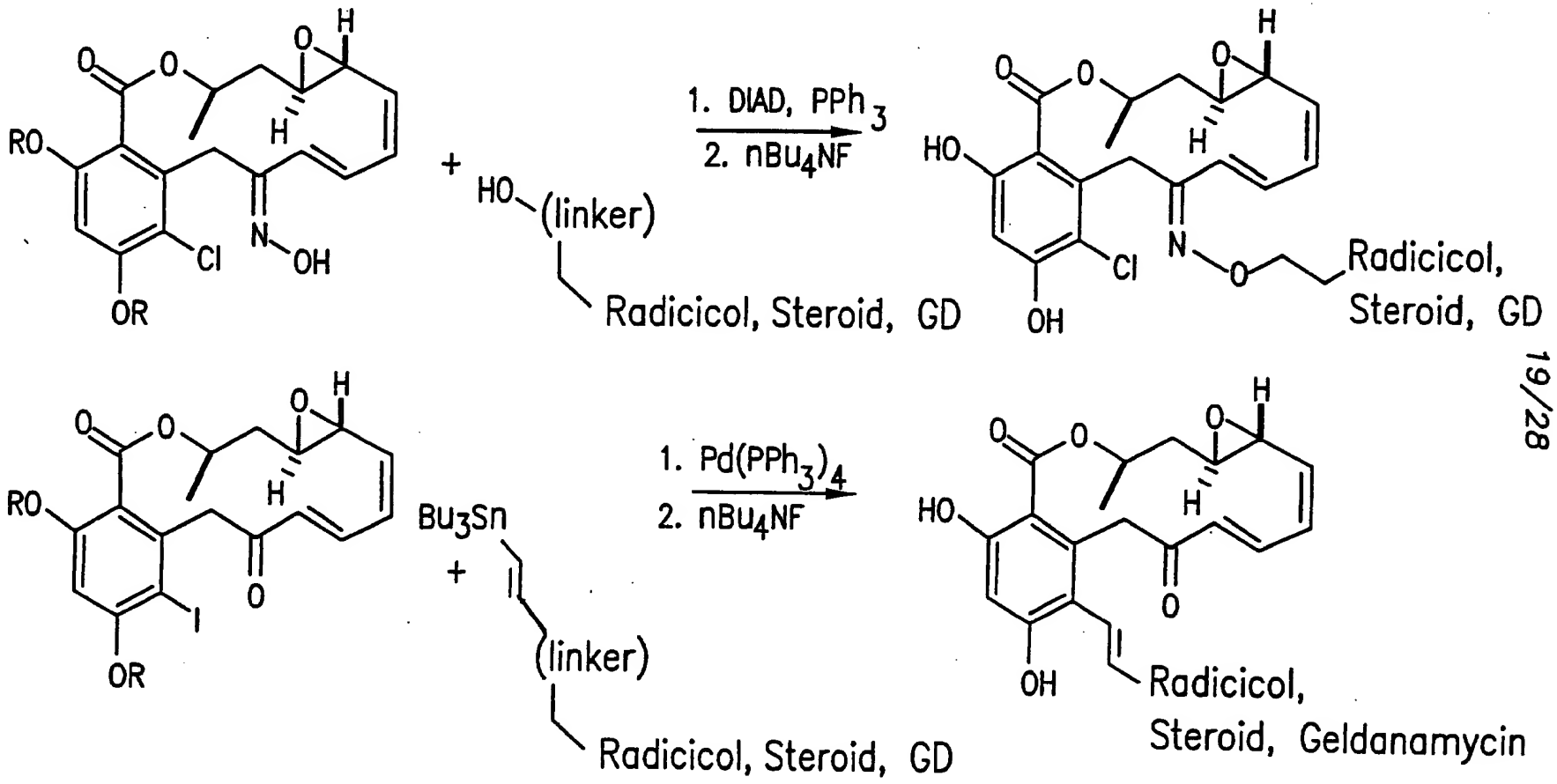


FIG. 16-1



TO FIG. 16-2

FROM FIG. 16–1

FIG. 16–2

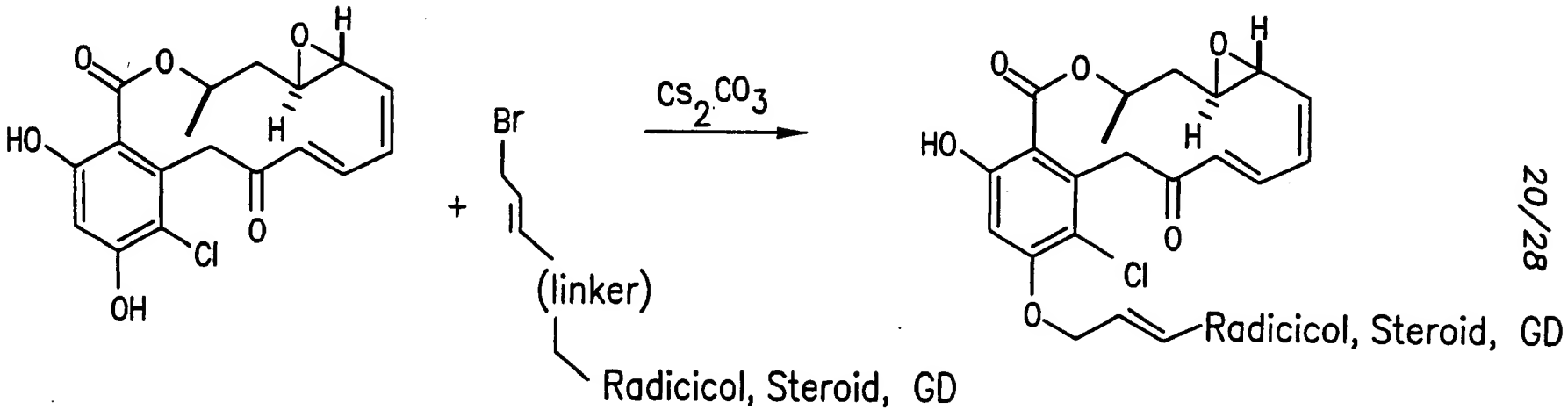
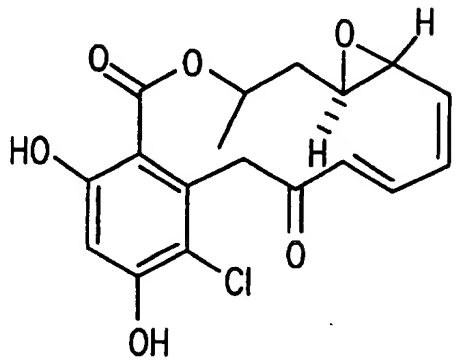
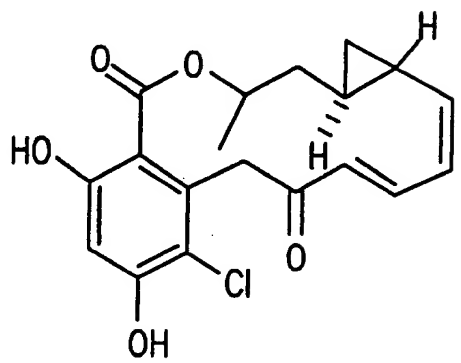


FIG. 17-1

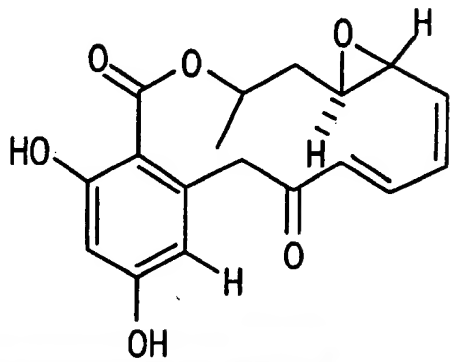
I. Radicicol



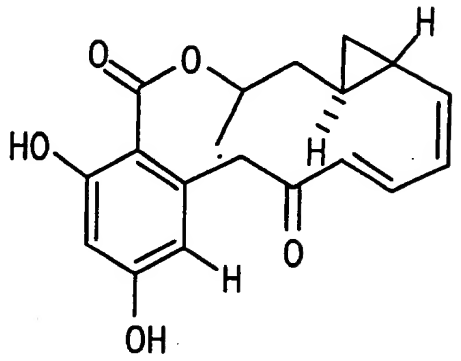
III. Cyclopropyl radicicol



II. Monocillin I



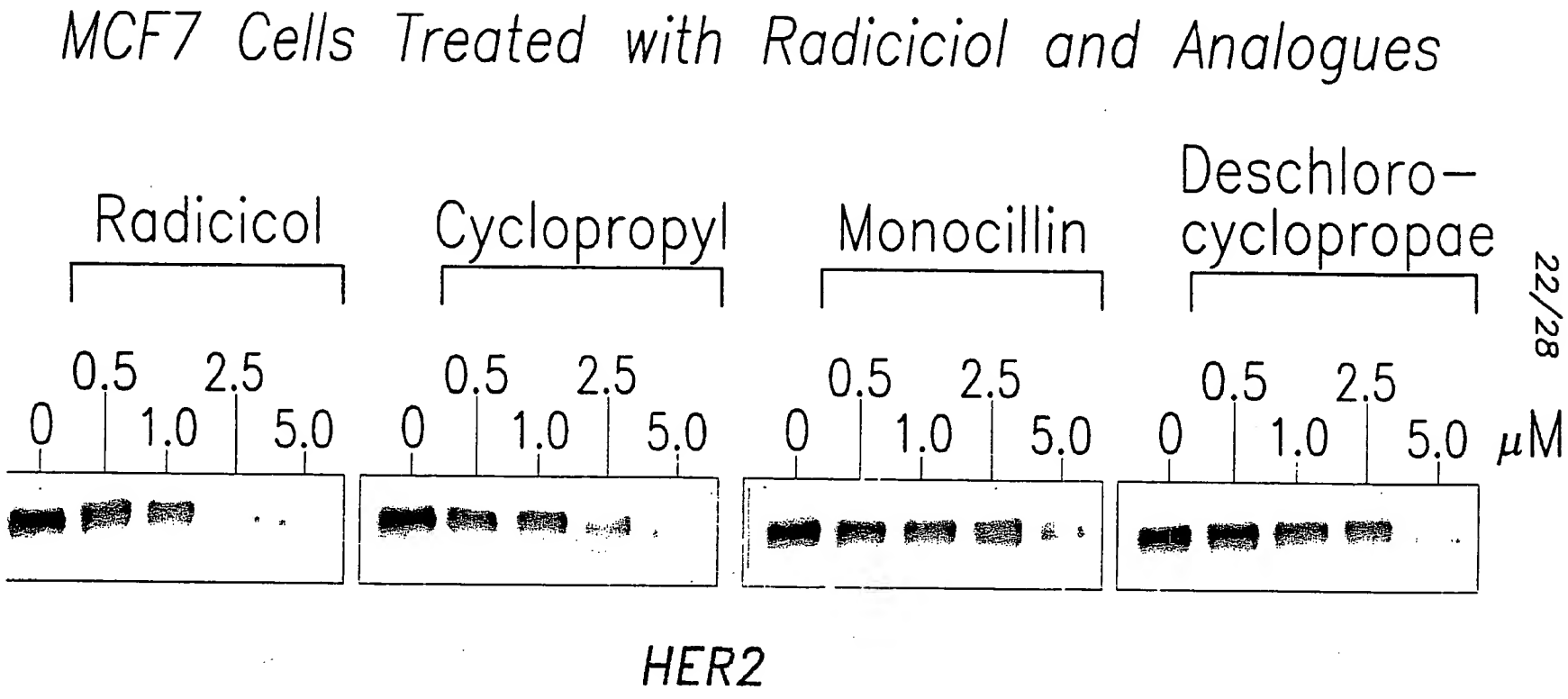
IV. Cyclopropyl monocillin



TO FIG. 17-2

FROM FIG. 17-1

FIG. 17-2

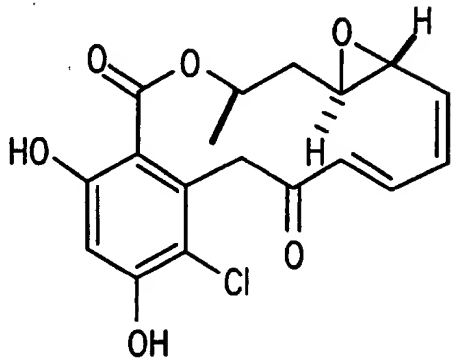


TO FIG. 17-3

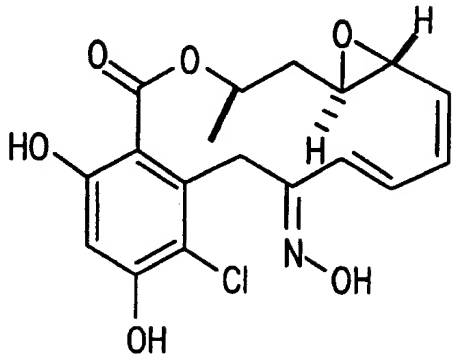
FROM FIG. 17-2

FIG. 17-3

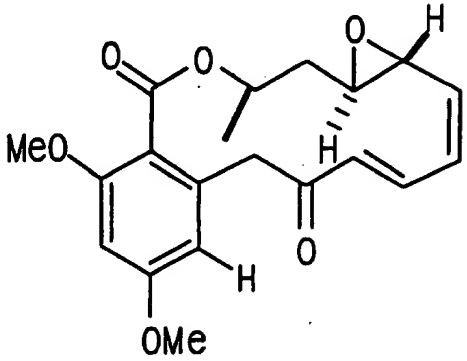
I. Radicicol



VII. Radicicol Oxime



V. Dimethyl Monocillin I



VI. Dimethyl Radicicol

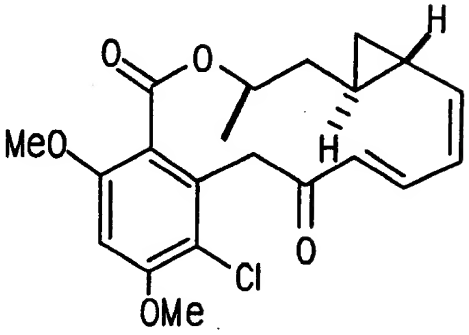
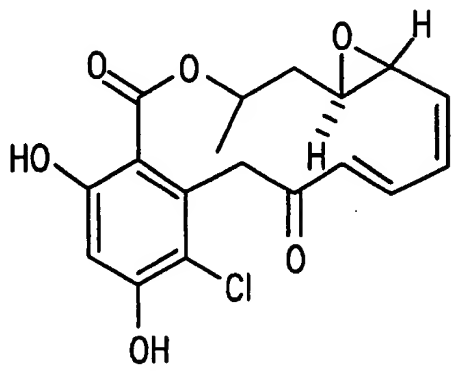
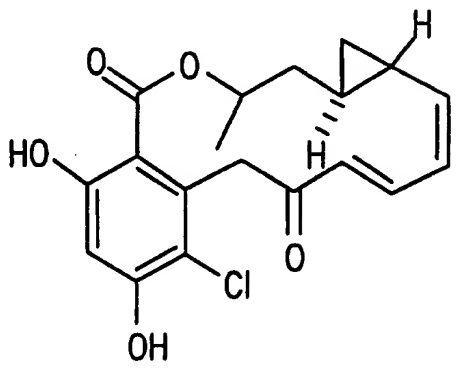


FIG. 18-1

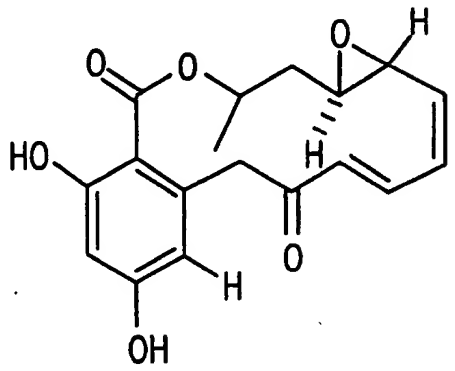
I. Radicicol



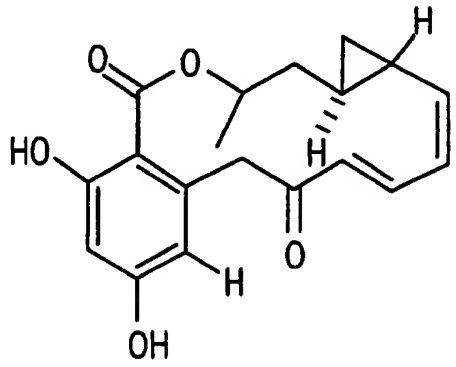
III. Cyclopropyl radicicol



II. Monocillin I



IV. Cyclopropyl monocillin

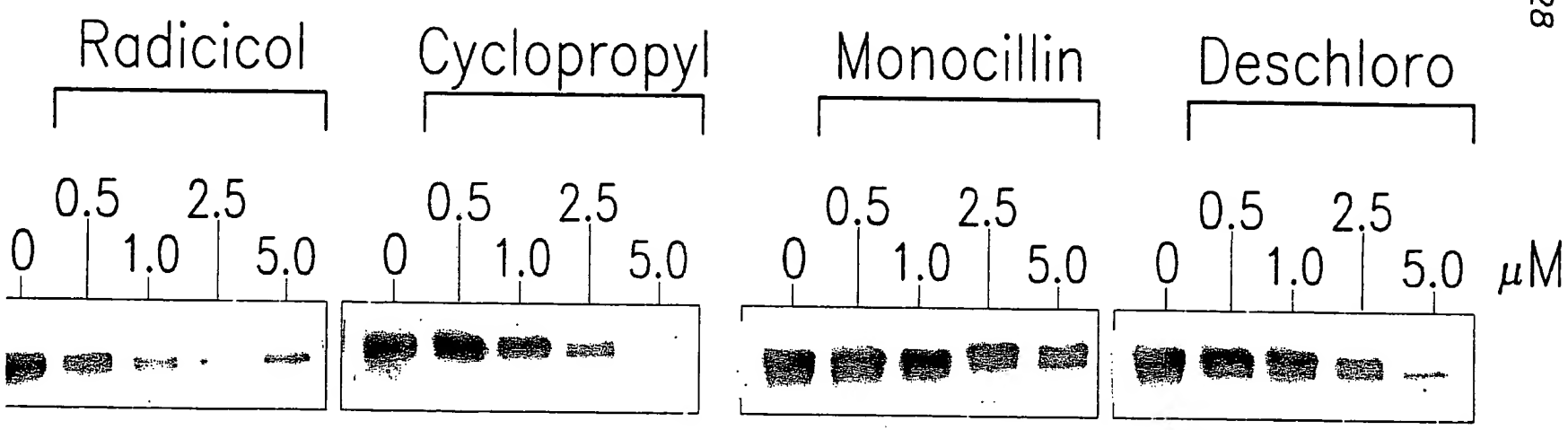


TO FIG. 18-2

FROM FIG. 18-1

FIG. 18-2

BT474 Cells Treated with Novel Radiciciols (24hrs.)



HER2

FIG. 19

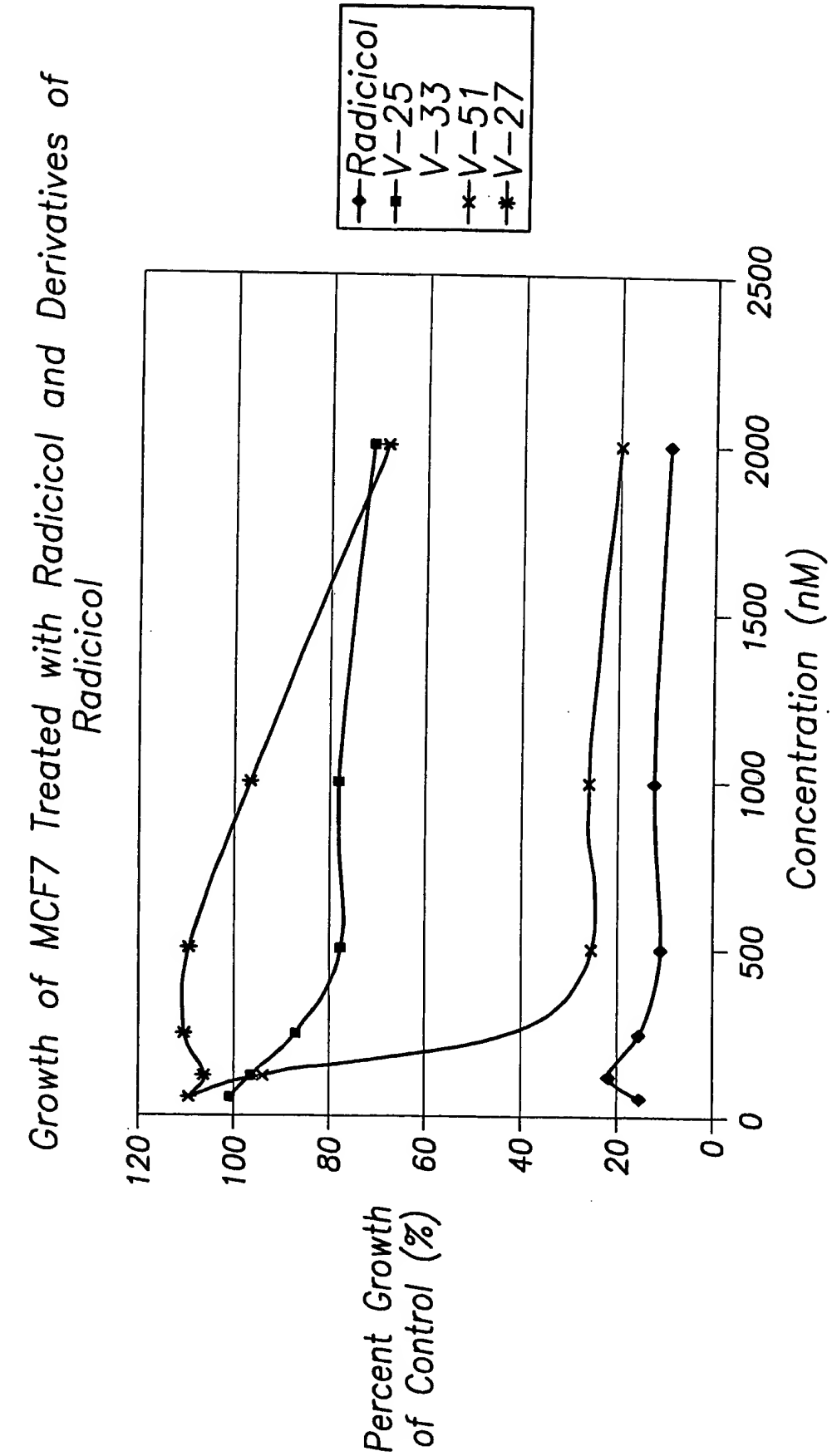

Growth of MCF7 Treated with Radicicol and Derivatives of Radicicol
Radicicol
V-25
V-33
V-51
V-27
Percent Growth of Control (%)
120
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Concentration (nM)

FIG.20

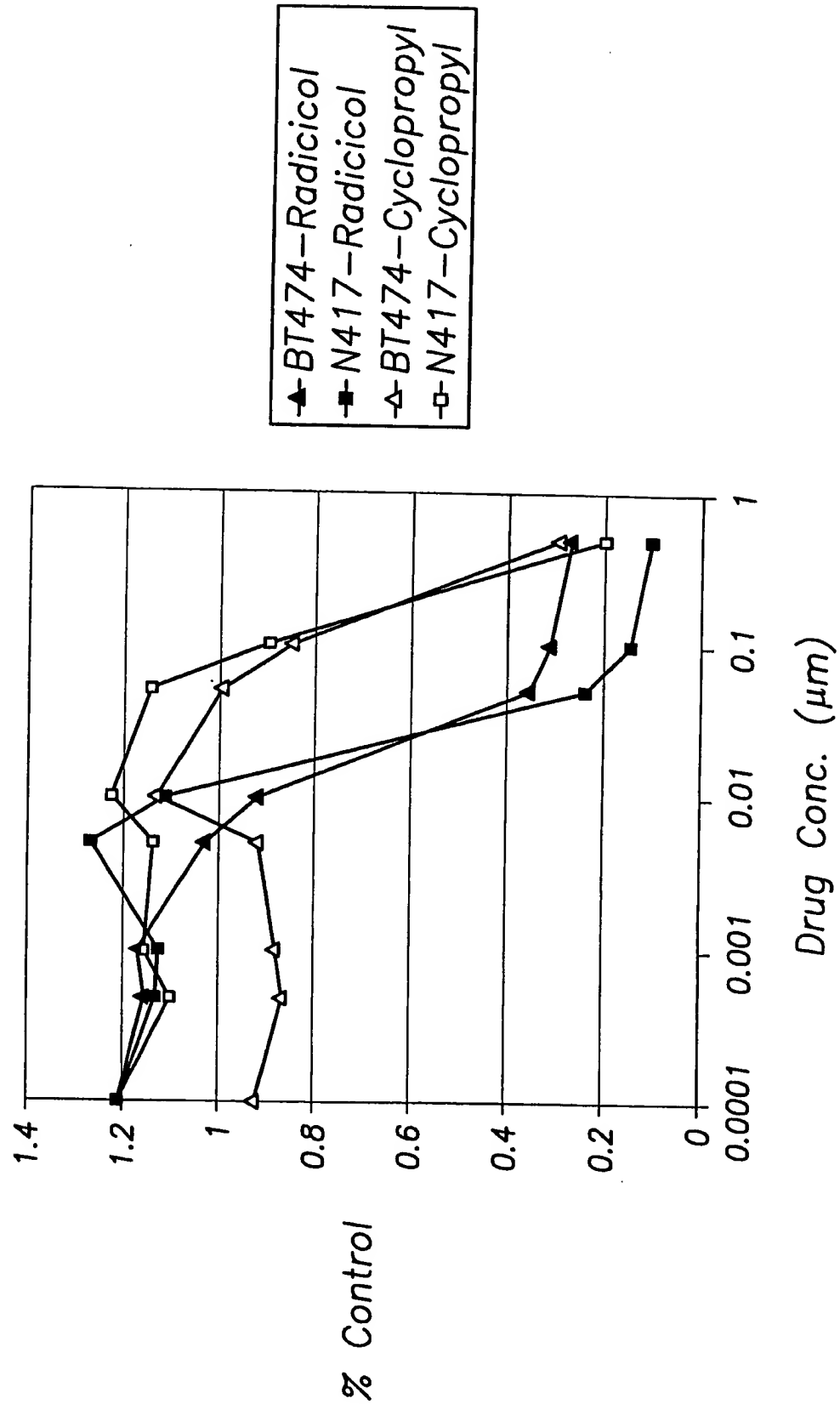
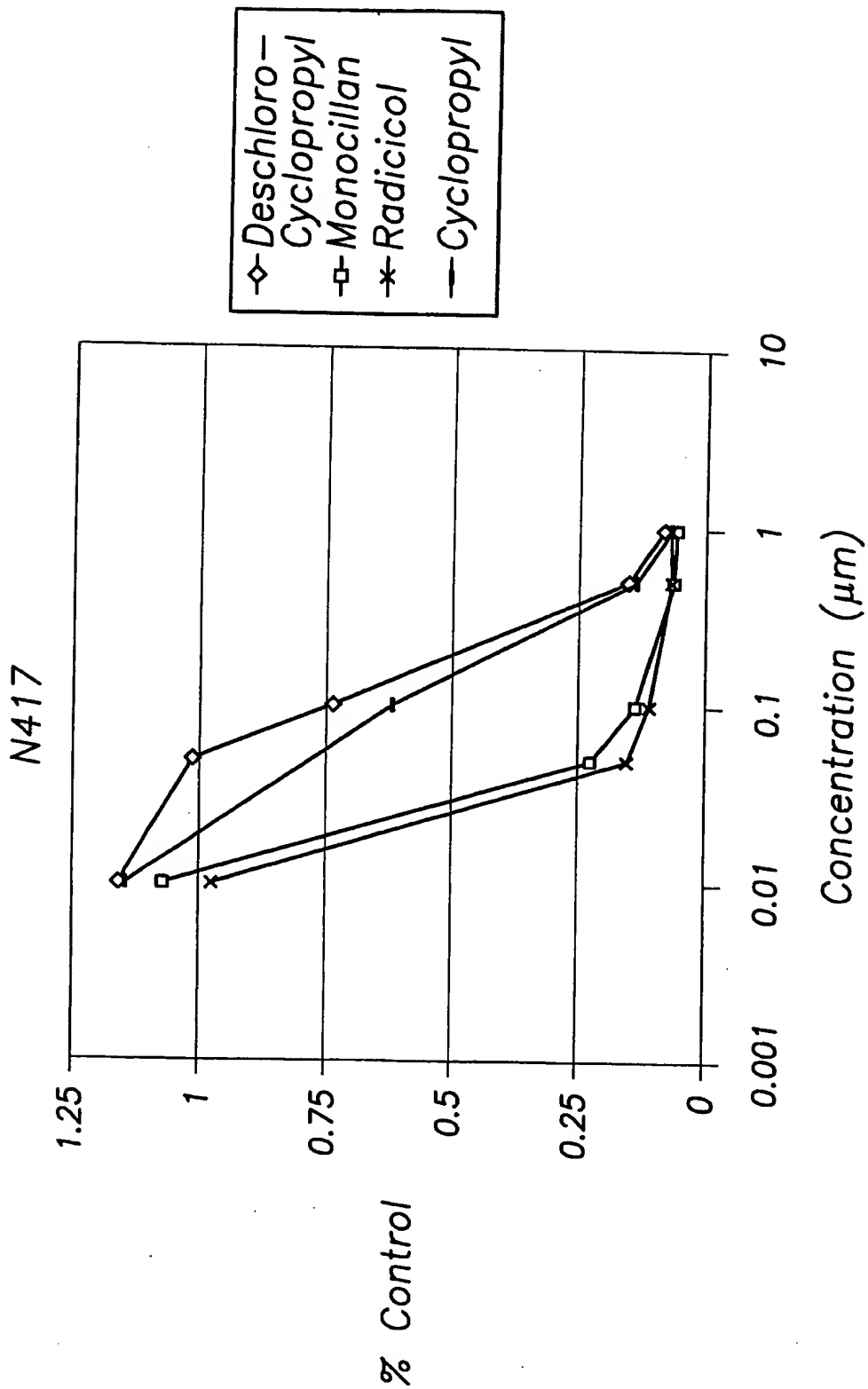

BT474–Radicicol
N417–Radicicol
BT474–Cyclopropyl
N417–Cyclopropyl
% Control
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.0001
0.001
0.01
0.1
1
Drug Conc. (μm)

FIG.21


N417
Deschloro–Cyclopropyl
Monocillan
Radicicol
Cyclopropyl
% Control
1.25
1
0.75
0.5
0.25
0
0.001
0.01
0.1
1
10
Concentration (µm)

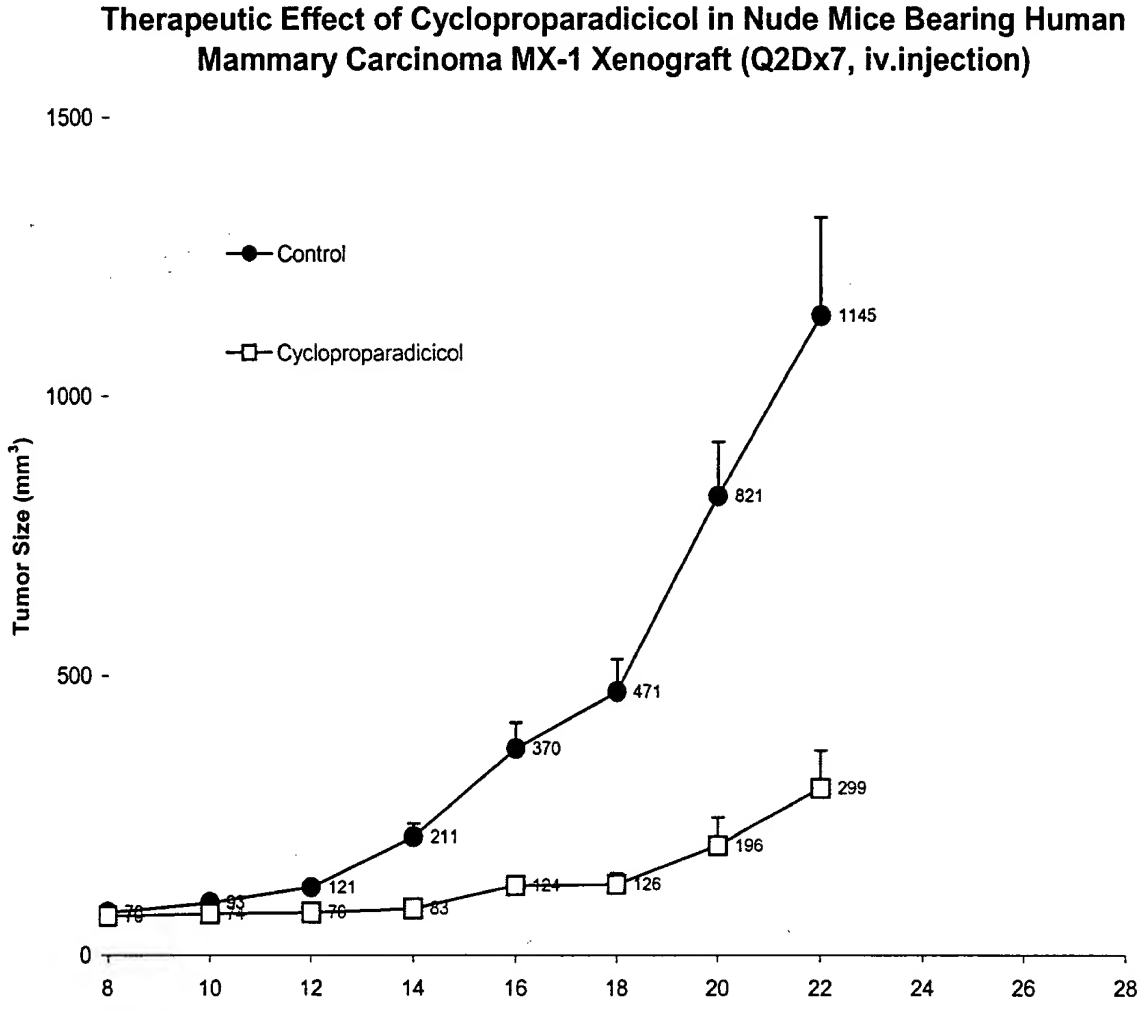

Therapeutic Effect of Cyclopropparadicicol in Nude Mice Bearing Human Mammary Carcinoma MX-1 Xenograft (Q2Dx7, iv.injection)
1500
1000
500
0
Tumor Size (mm3)
Control
Cyclopropparadicicol
1145
821
471
370
299
211
196
121
126
124
93
83
76
74
70
8
10
12
14
16
18
20
22
24
26
28

FIG. 22

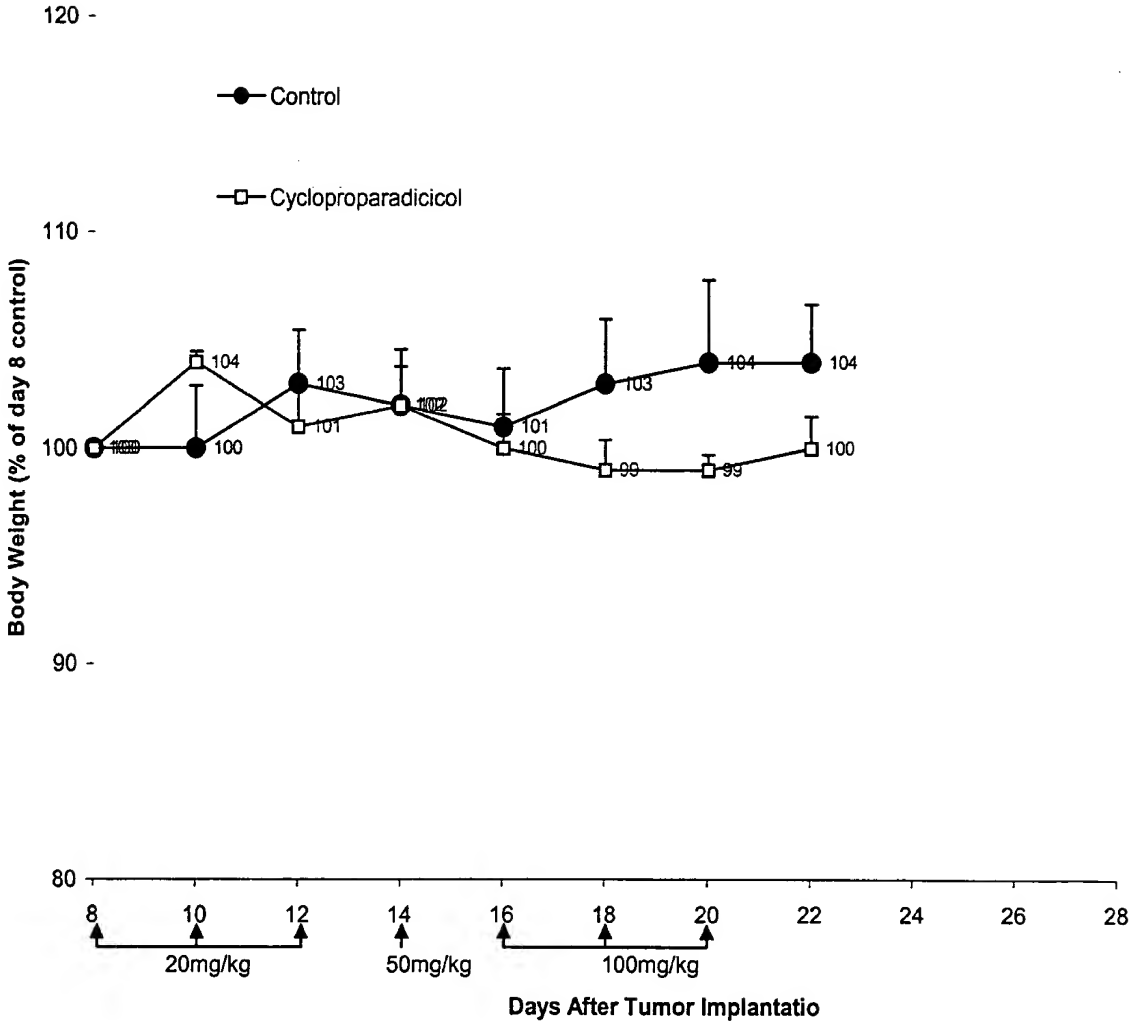

120
110
100
90
80
Control
Cyclopropradicicol
Body Weight (% of day 8 control)
104
100
103
101
102
101
100
103
99
104
99
104
100
8
10
12
14
16
18
20
22
24
26
28
20mg/kg
50mg/kg
100mg/kg
Days After Tumor Implantatio

FIG. 23

MX-1 tumors
12 hrs following a 6 hr CIVI

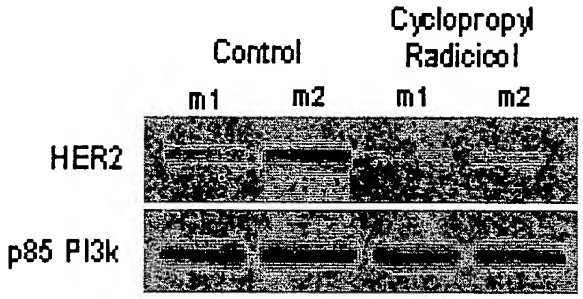
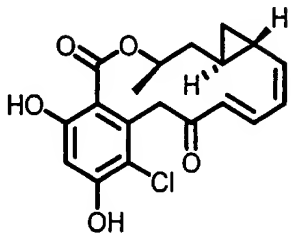
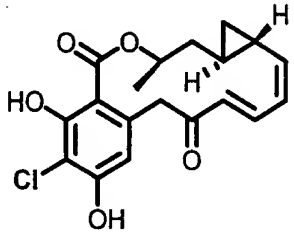
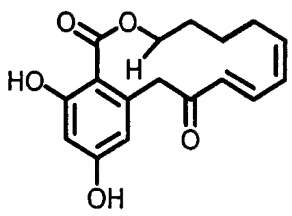


FIG. 24

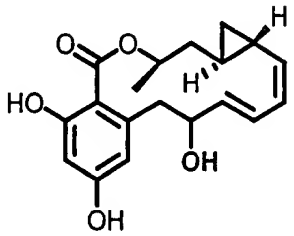
IC_{50} of Growth Inhibition of Different Tumor Cell lines

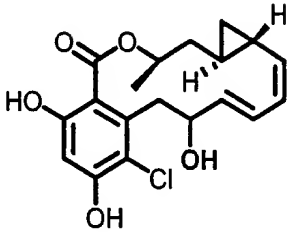


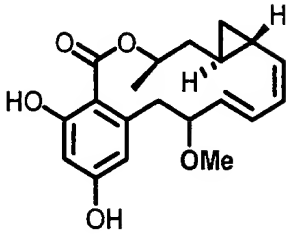




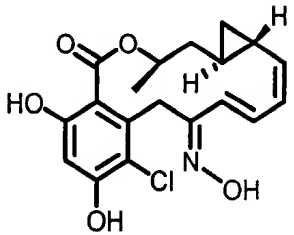
Cell lines			
MCF-7	54 nM	>500 nM	>500 nM
CCRF-CEM	42 nM		
CCRF-CEM/Vinblastin resistant	32 nM		

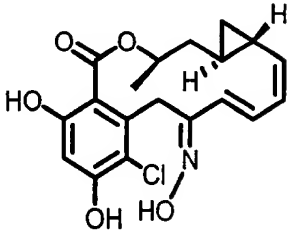






Cell lines			
MCF-7	150 nM, >500 nM	390 nM	
CCRF-CEM	208 nM		>500 nM
CCRF-CEM/Vinblastin resistant	209 nM		>5 μM





Cell lines		
MCF-7	98 nM	282 nM

FIG. 25

Degradation of HER2 by Cycloproparadicicol Analogues

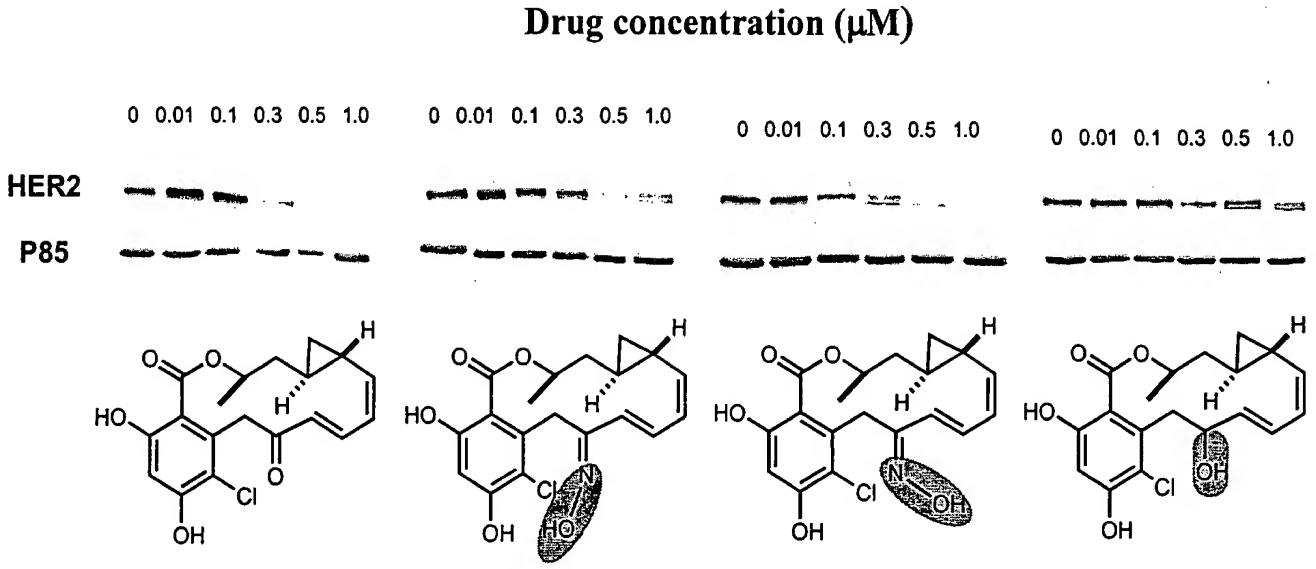


FIG. 26

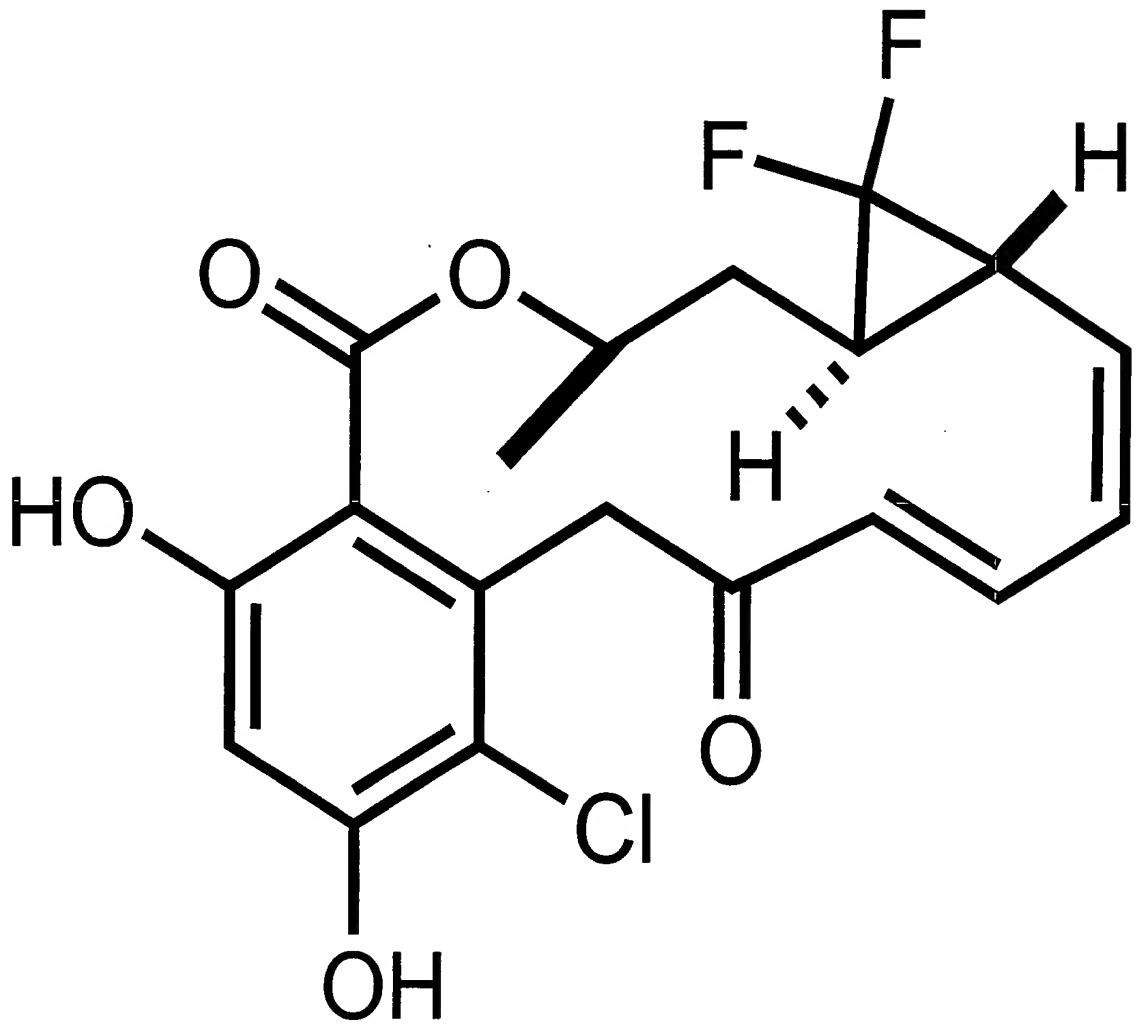


FIG. 27